Pharmacodynamics: actual data

How shall we dose

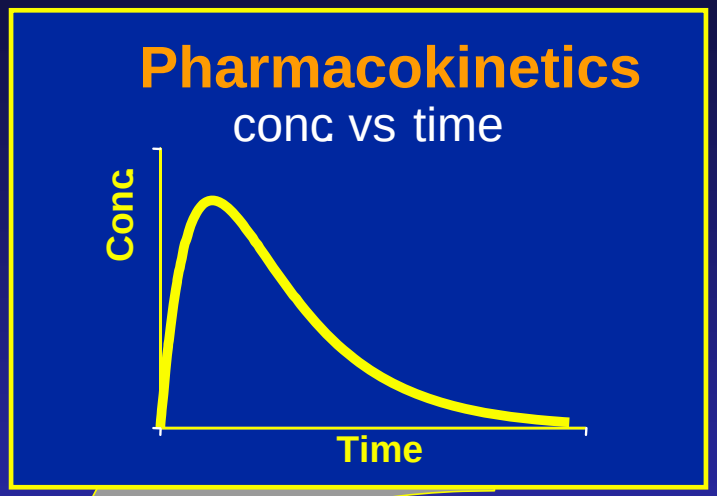
time-dependent

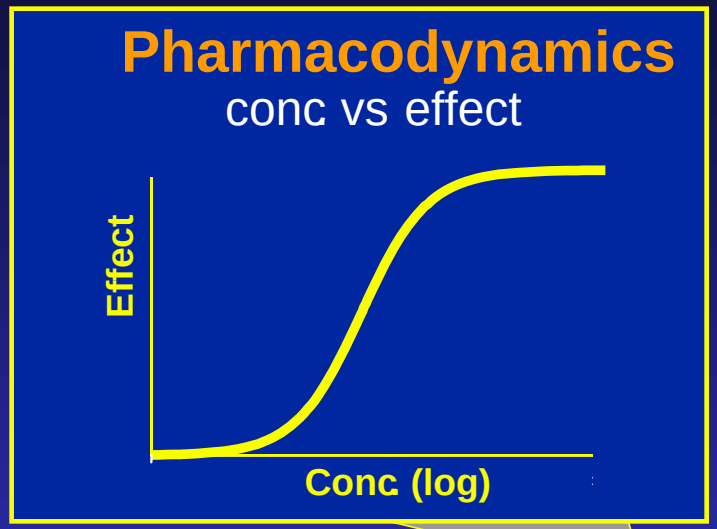
concentration-dependent

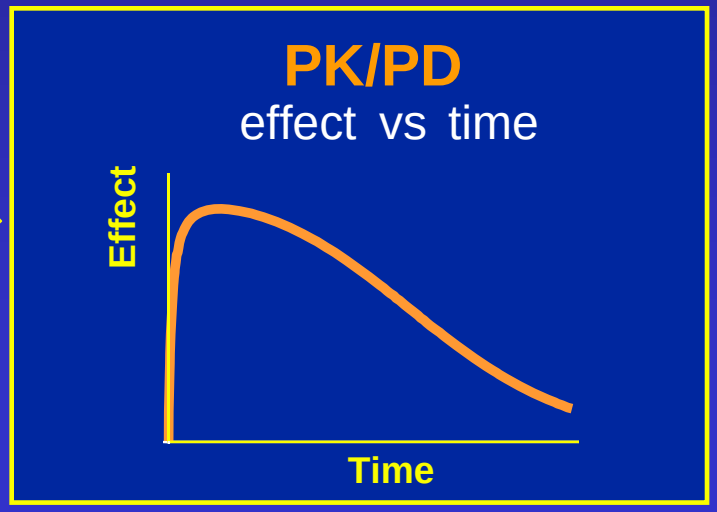
antibiotics ?

With the support of *Wallonie-Bruxelles-International*

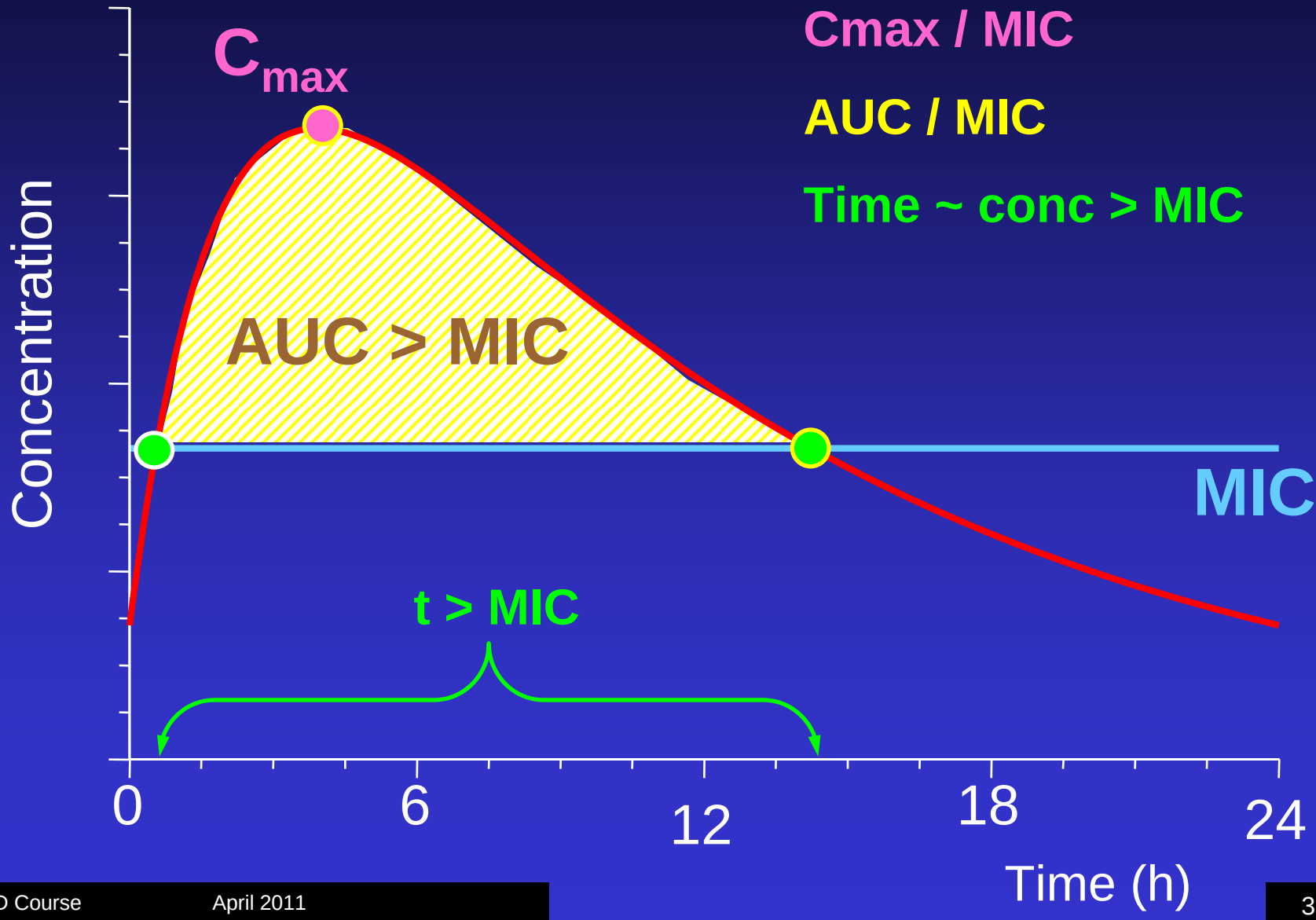
from pharmacokinetics to pharmacodynamics...







from pharmacokinetics to pharmacodynamics...



Main PK/PD properties of antibiotics

Available antibiotics can be divided in 3 groups :

- time - dependent (T > MIC)
- AUC / MIC - dependent
- both AUC / MIC and peak / MIC -dependent

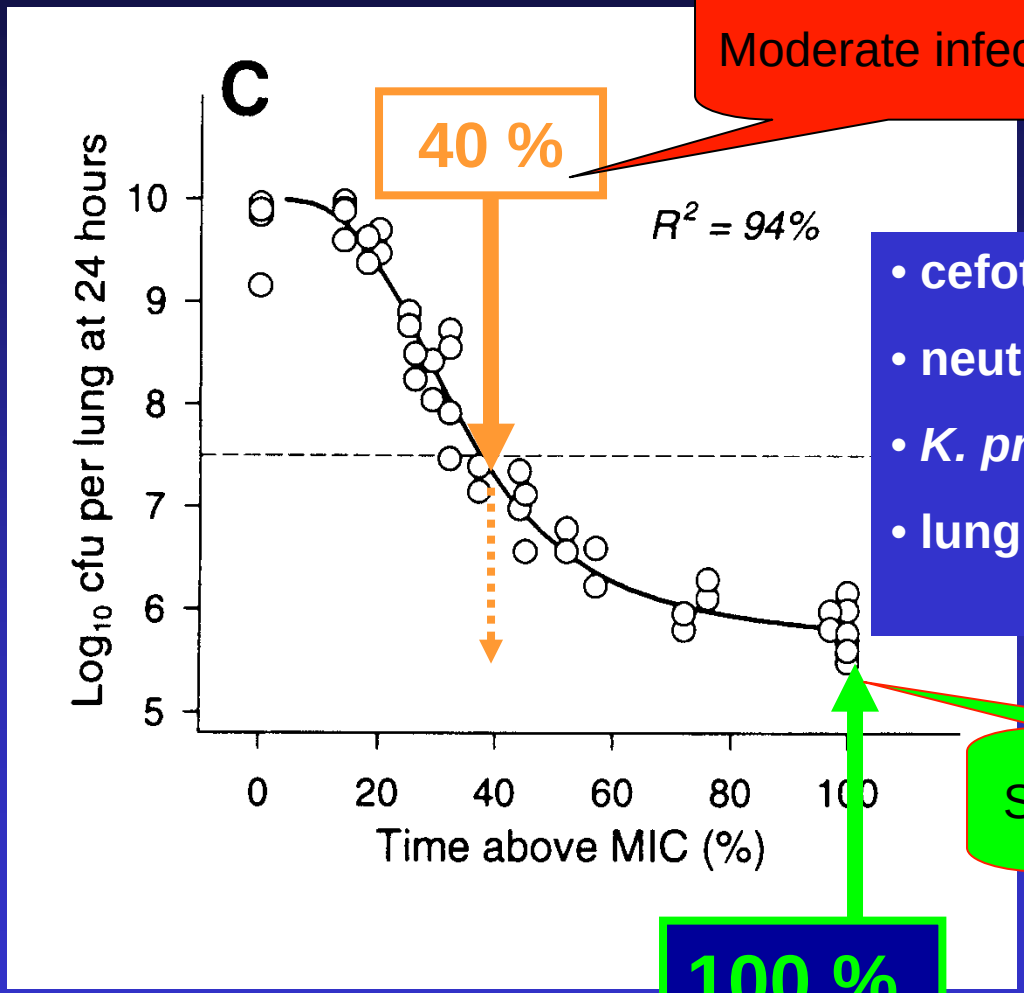
Antibiotics Group # 1

(after W.A. Craig, 2000; revised 2002 and 2003)

1. **Antibiotics with time-dependent effects and no or little persistent effects**

AB	PK/PD parameter	Goal
β-lactams	Time above MIC	Maximize the exposure time

How long should you stay above the MIC ?



Moderate infections

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

Serious infections

100 %

More experimental data with penicillins, cephalosporins and carbapenems ...

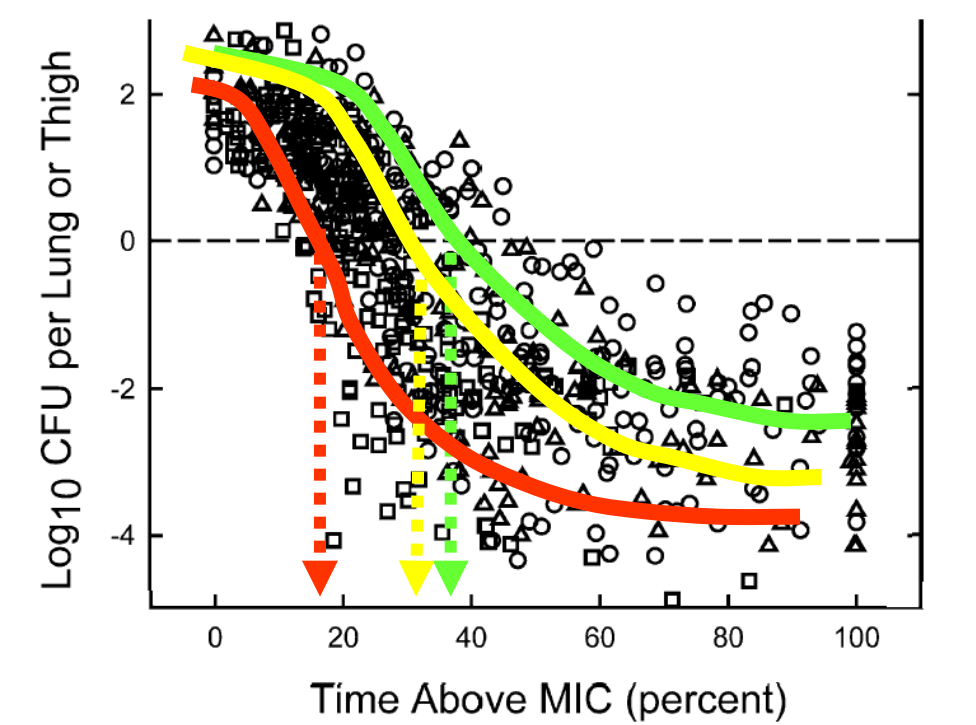


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung fo[r] various path[o]gens following 24 h of therapy with different doses o[f] penicillins (△), cephalosporins (○), and carbapenems (□).

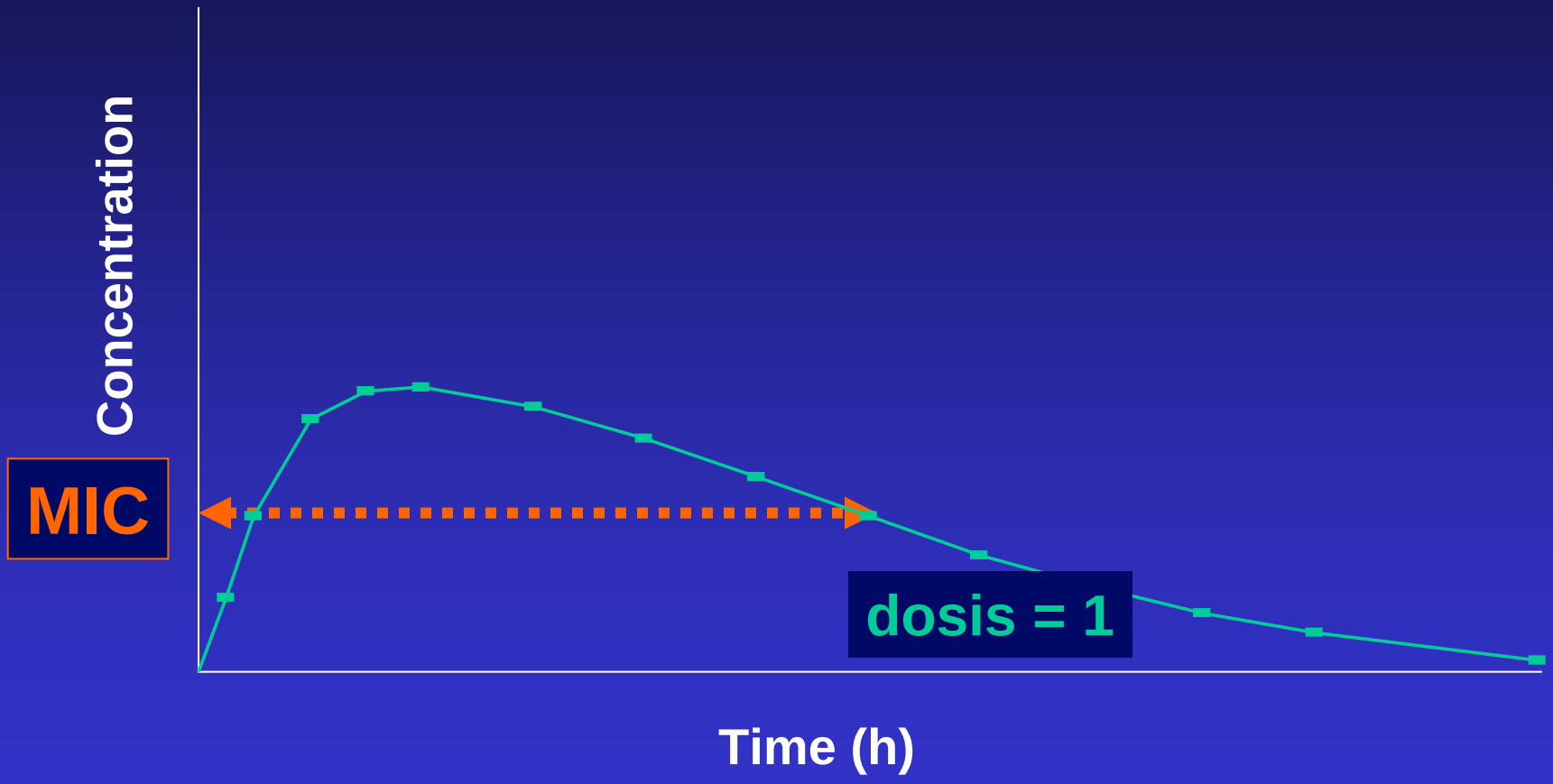
different pathogens

- same shape of dose response
- diff. in **T > MIC** for a static effect (penicill. > carbap.)
- diff **E_{max}** (penicill. < carbap.)

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

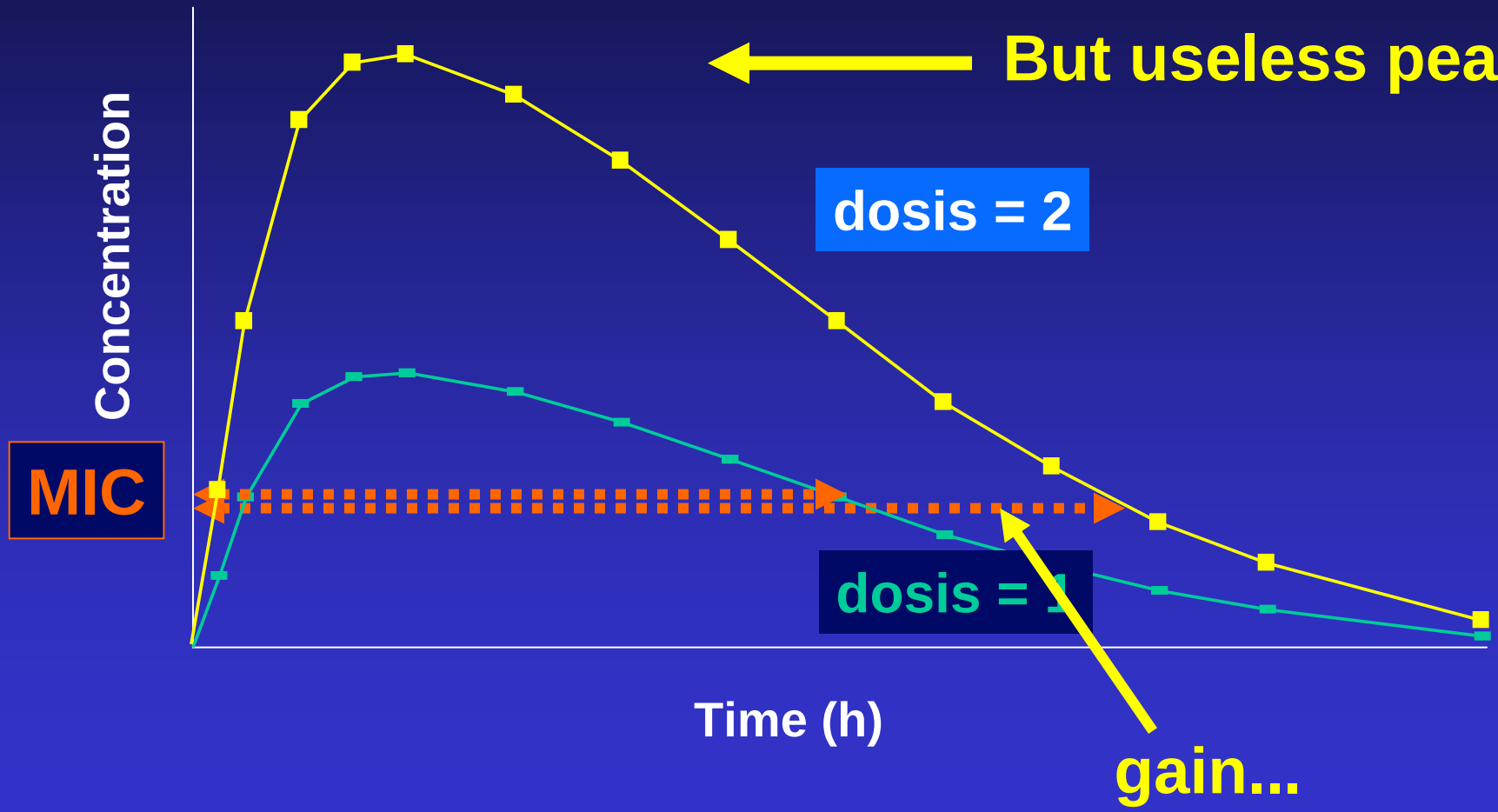
How to optimize T > MIC ?

1. Increase the unitary dosis ?



How to optimize T > MIC ?

1. Increase the unitary dosis ?

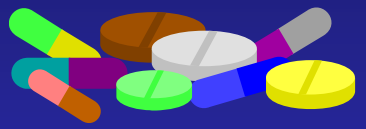


How to optimize T > MIC ?

2. Increase the number of administrations ?

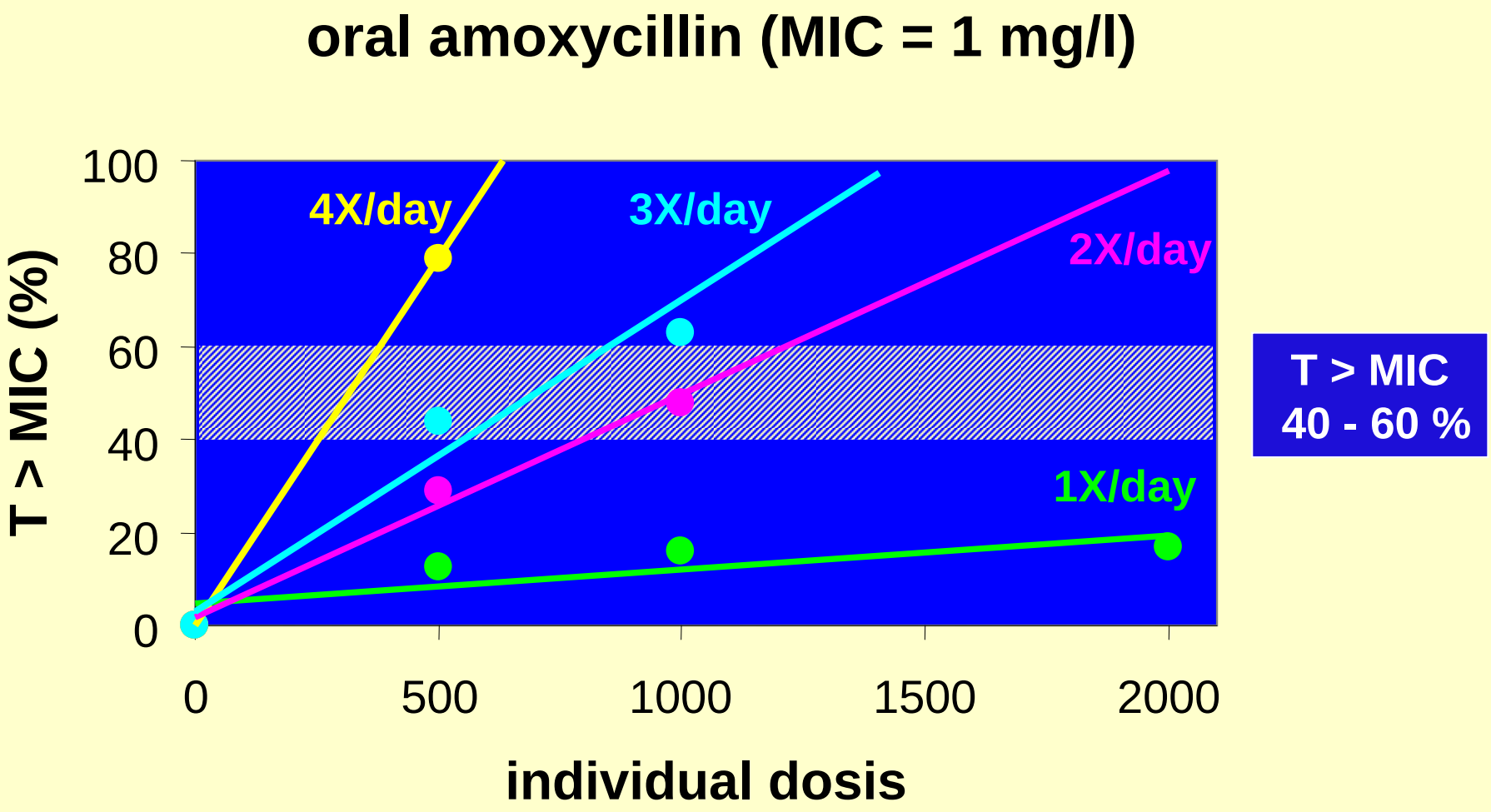
β-lactams : applications...

- Respiratory tract infections (oral route)…



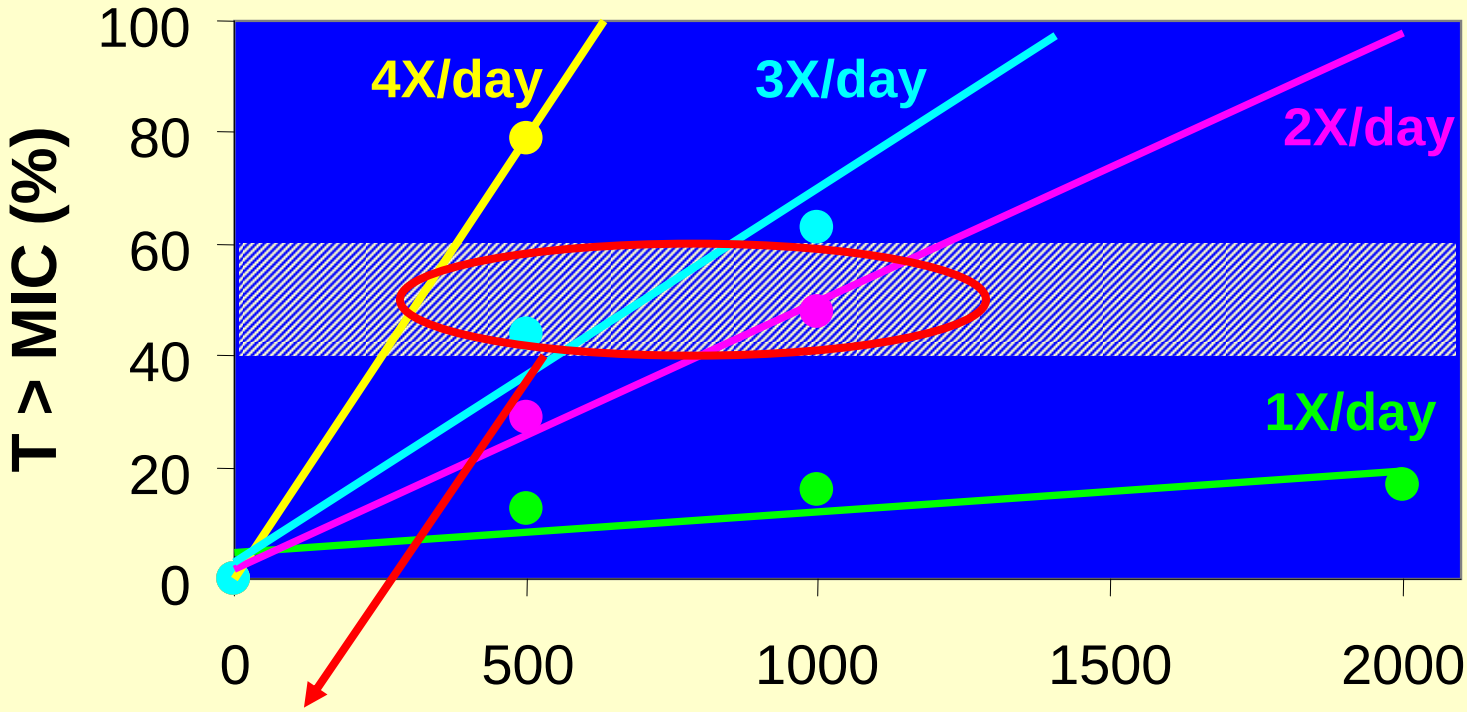
- Serious infections (intravenous route)

Optimizing dosage for amoxycillin



Optimizing dosage for amoxycillin

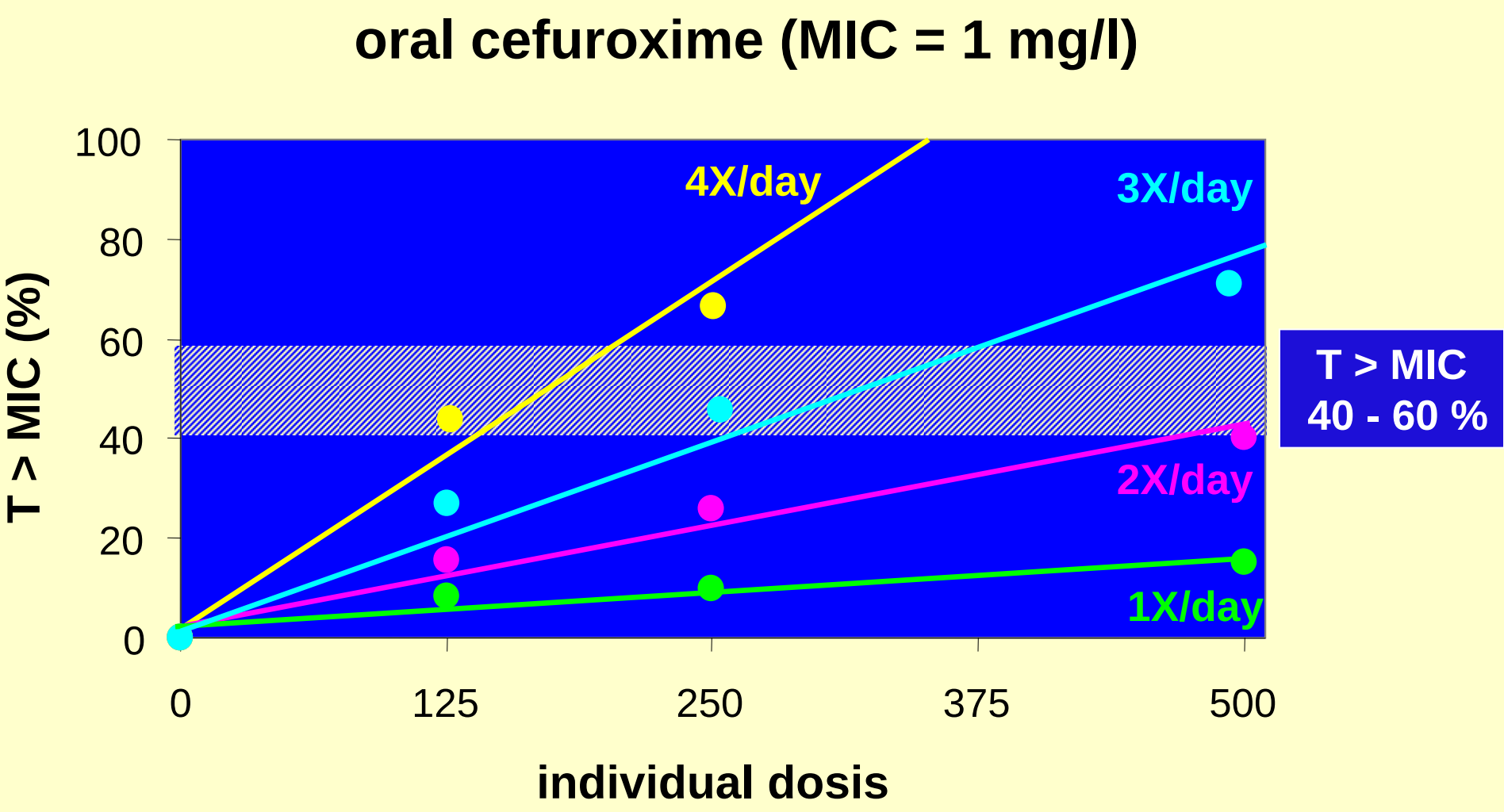
oral amoxycillin (MIC = 1 mg/l)



T > MIC
40 - 60 %

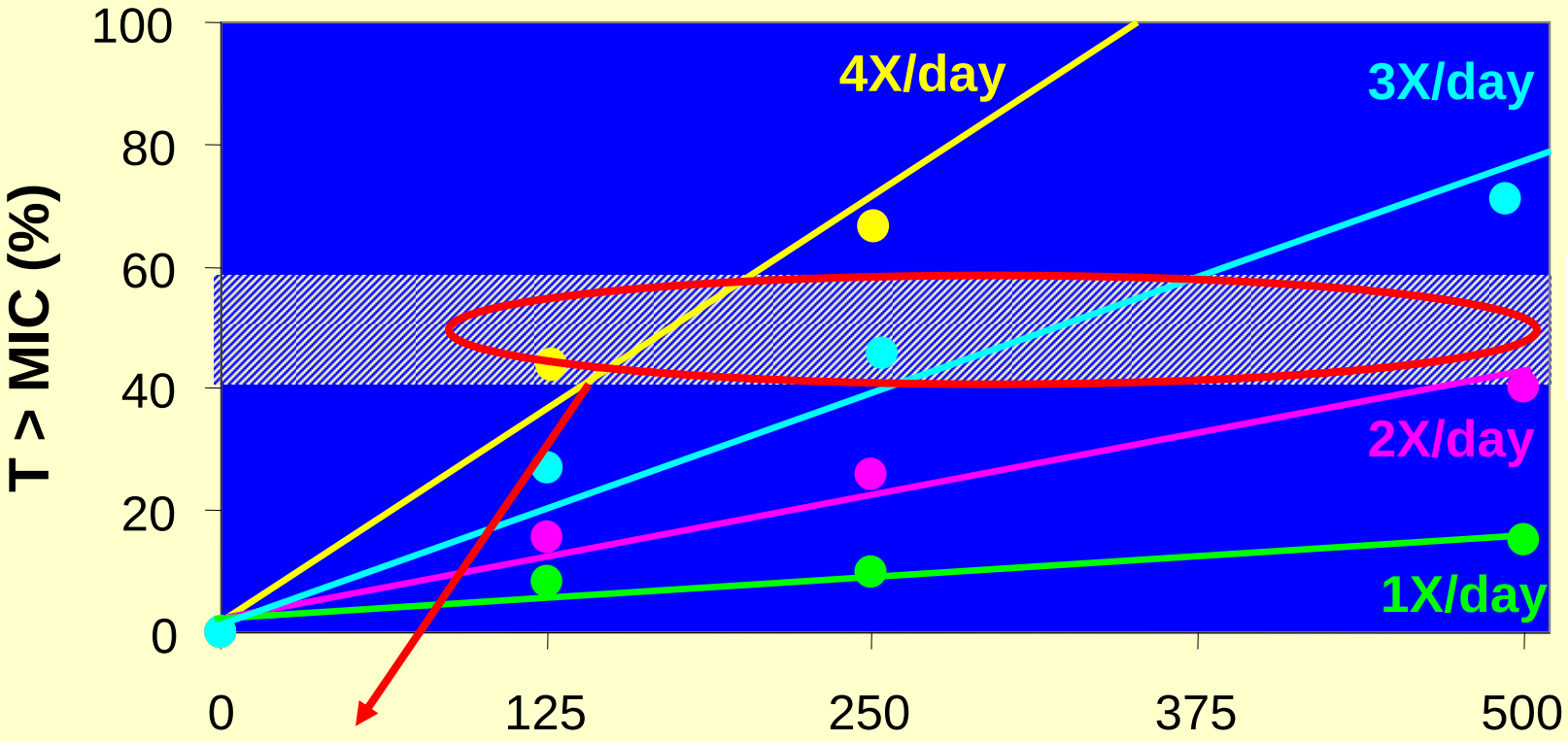
Appropriate dose =
500 mg 3-4 X/d or 1000 mg 2 X/d

Optimizing dosage for cefuroxime



Optimizing dosage for cefuroxime

oral cefuroxime (MIC = 1 mg/l)



Oral β- lactams and *S. pneumoniae*

An MIC of ~ 2 µg/ml is the limit that you can cover in optimal conditions, i.e. with a 3 x / day administration and a total daily dosis of

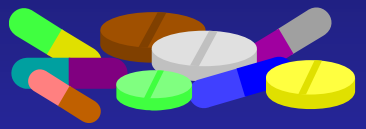
- 3 g for amoxicillin
- 1-1.5 g for cefuroxime-axetil

PK/PD breakpoint for oral β- lactams:

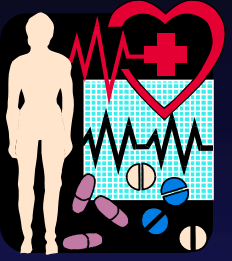
MIC < 2 µg/ml

β-lactams : applications...

- Respiratory tract infections (oral route)…



- Serious infections (intravenous route)



Typical pharmacokinetics of an IV β-lactam

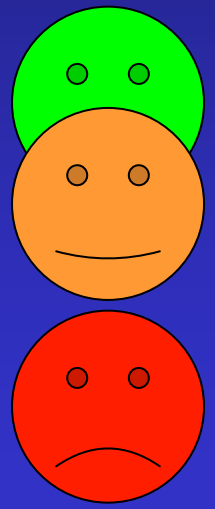
time	serum concentration for		
(hours)	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

* Single administration unique; half-life 2h ; V_d = 0.2 l/kg

Typical pharmacokinetics of an IV β-lactam

time (hours)	serum concentration for 0.5 g	1 g	2 g
2	25		
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

Where would you like to be ?



* Single administration unique; half-life 2h ; V_d = 0.2 l/kg

Optimisation of IV β-lactams for "difficult" organisms

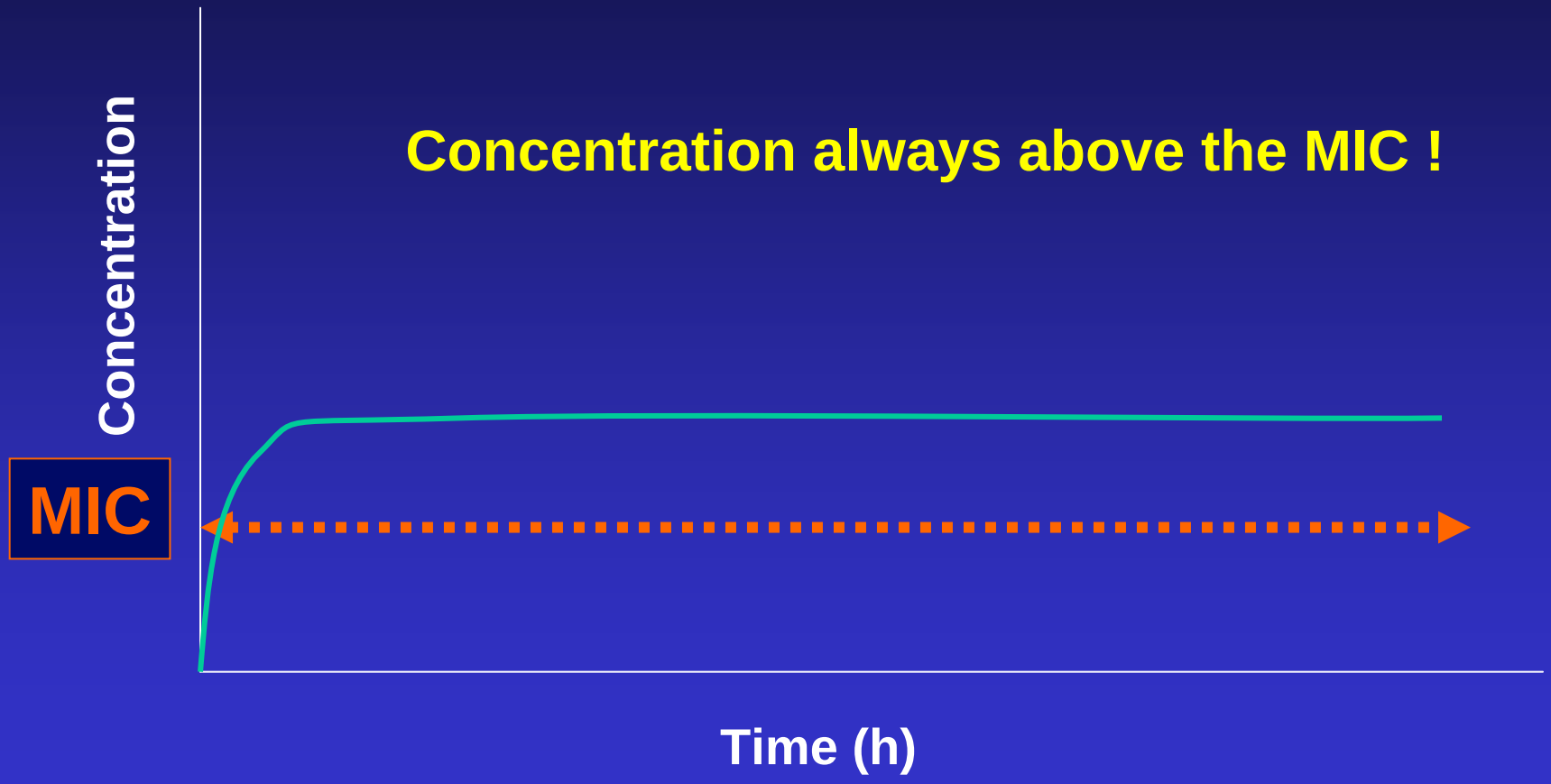
- 2 g every 12 h → **T > MIC = 100 % if MIC ≤ 3 mg/L !**
- 2 g every 8 h → **T > MIC = 100 % if MIC ≤ 12 mg/L**

More frequent administrations is the best way to increase the activity of β-lactams in difficult-to-treat infections...

→ **PK / PD breakpoint for IV β-lactams : MIC < 8 µg/ml**

Can we do still better ?

3. Continuous infusion



Continuous infusion: the solution ?

Yes :

- Optimized mode of administration
- Possibility to obtained stable concentrations as high as 20 to 40 mg/L

But be careful …

- To the stability of the molecule
  - the β-lactam ring is intrinsically breakable …
    ➔ temperature !!!
- To incompatibilities with other molecules also administered by continuous infuison

➔ **Caution rules need to be respected ….**

Continuous infusion: the solution ?

Yes :

- Optimized mode of administration
- Possibility to obtained stable concentrations as high as

There will be a special course on β-lactams by continuous infusion !!

- To the stability of the molecule
  - the β-lactam ring is intrinsically breakable …
    ➔ temperature !!!
- To incompatibilities with other molecules also administered by continuous infuison

➔ **Caution rules need to be respected ….**

Antibiotics Group # 2

(after W.A. Craig, 2000; revised 2002 and 2003)

2. Antibiotics with time-dependent effects, no or little influence of concentration, but marked persistent effects

AB	PK/PD parameter	Goal
glycopeptides tetracyclines macrolides streptogramins oxazolidinones	AUC / MIC	optimize the amount of antibiotic

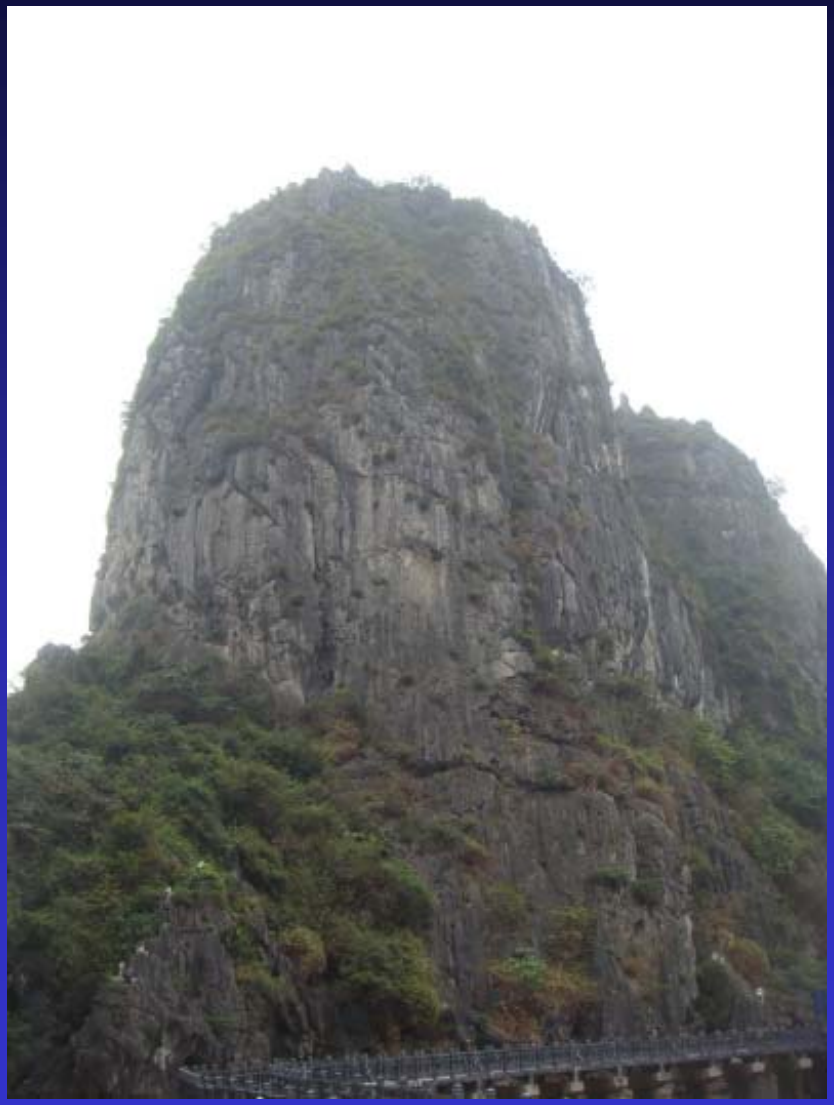
Antibiotics Group # 3

(after W.A. Craig, 2000; revised 2002 and 2003)

3. Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)

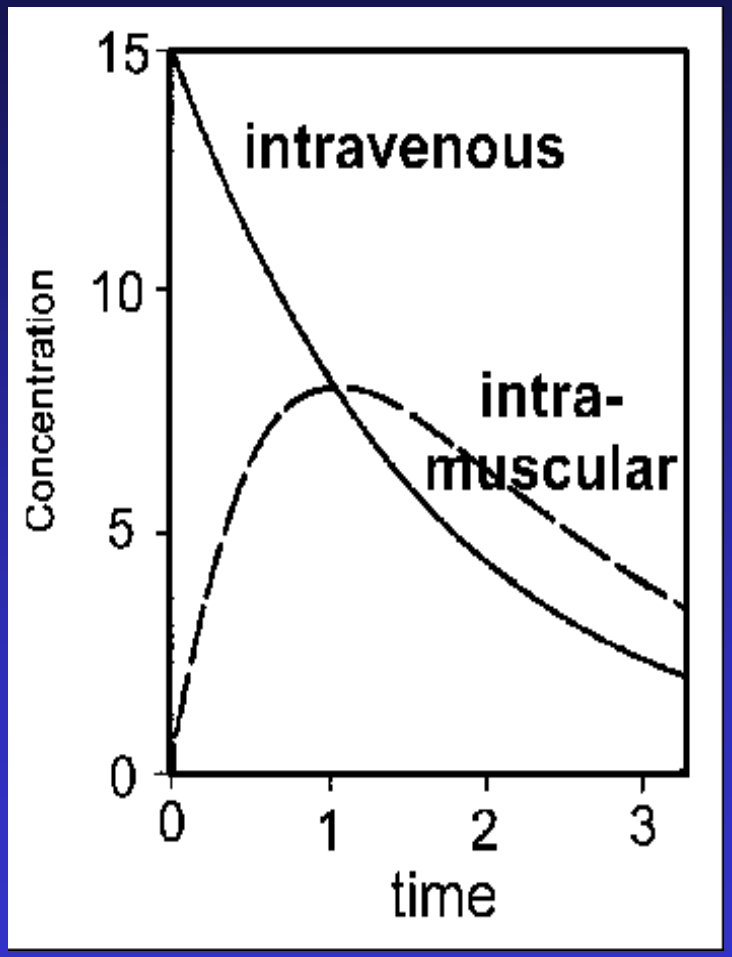
AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin	**Peak and AUC / MIC**	**optimize the peak and the amount of antibiotic**

Aminoglycosides: get a peak !



Aminoglycosides: get a peak !

Peak/MIC > 8



1. **Appropriate mode of administration**

   ⇨ **IV route**

2. Calculation of the necessary peak value

⇨ **minimal peak: = MIC x 8**

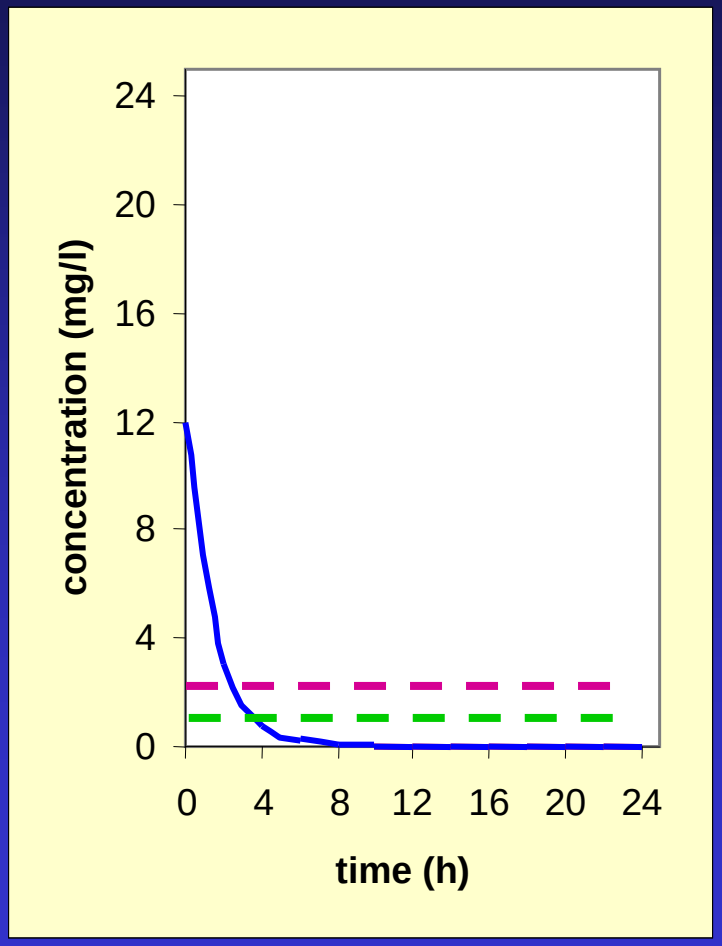
3. Calculation of the adequate dosis

⇨ **peak = dosis / Vd**

⇨ **dosis = peak x Vd**

⇨ **dosis = MIC x 8 x Vd**

Aminoglycosides: get a peak !



3 mg / kg - 1 X day

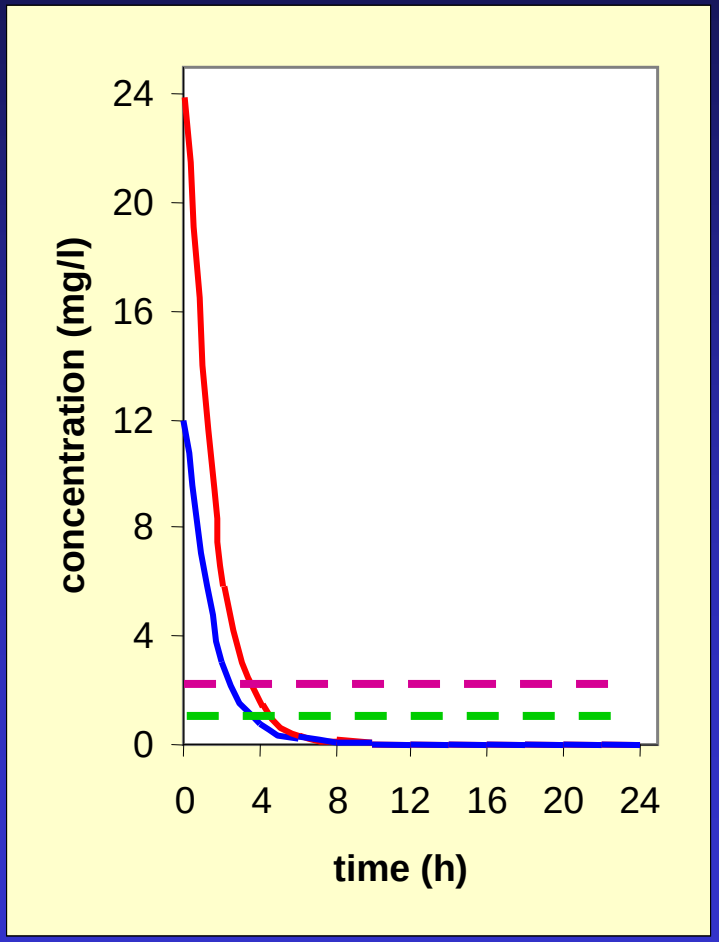
MIC = 2 → peak/MIC ~ 6

MIC = 0.5 → peak/MIC ~ 24

* aminoglycoside with half-life= 1 h and V_d = 0.25 l/kg

Aminoglycosides: get a peak !

Increase the dose!



6 mg / kg - 1 X jour

MIC = 2 → peak/MIC ~ 12

MIC = 0.5 → peak/MIC ~ 48

* aminoglycoside with half-life= 1 h and V_d = 0.25 l/kg

Aminoglycosides: which dosis for which MIC ?

dosis (mg/kg)	peak (mg/L) for V_d = 0.25 l/kg	peak/MIC if MIC = 4	2	1	0.5
1	4	1	2	4	8
2	8	2	4	8	16
3	12	3	6	12	24
4	16	4	8	16	32
6	24	6	12	24	48
8	32	8	16	32	64

Aminoglycosides: which dosis for which MIC ?

dosis (mg/kg)	peak (mg/L) for V_d = 0.25 l/kg	peak/MIC if MIC = 4	2	1	0.5
3	12	3	6	12	24
4	16	4	8	16	32
6	24	6	12	24	48
8	32	8	16	32	64

There will be a special course on aminoglycosides dose optimization !

Optimization of aminoglycoside usage

do not try to treat with aminoglycosides bacteria with MIC

- > 2 µg/ml for molecules with maximal daily dosis of 6 mg/kg
- > 4 µg/ml for molecules with maximal daily dosis of 15 mg/kg

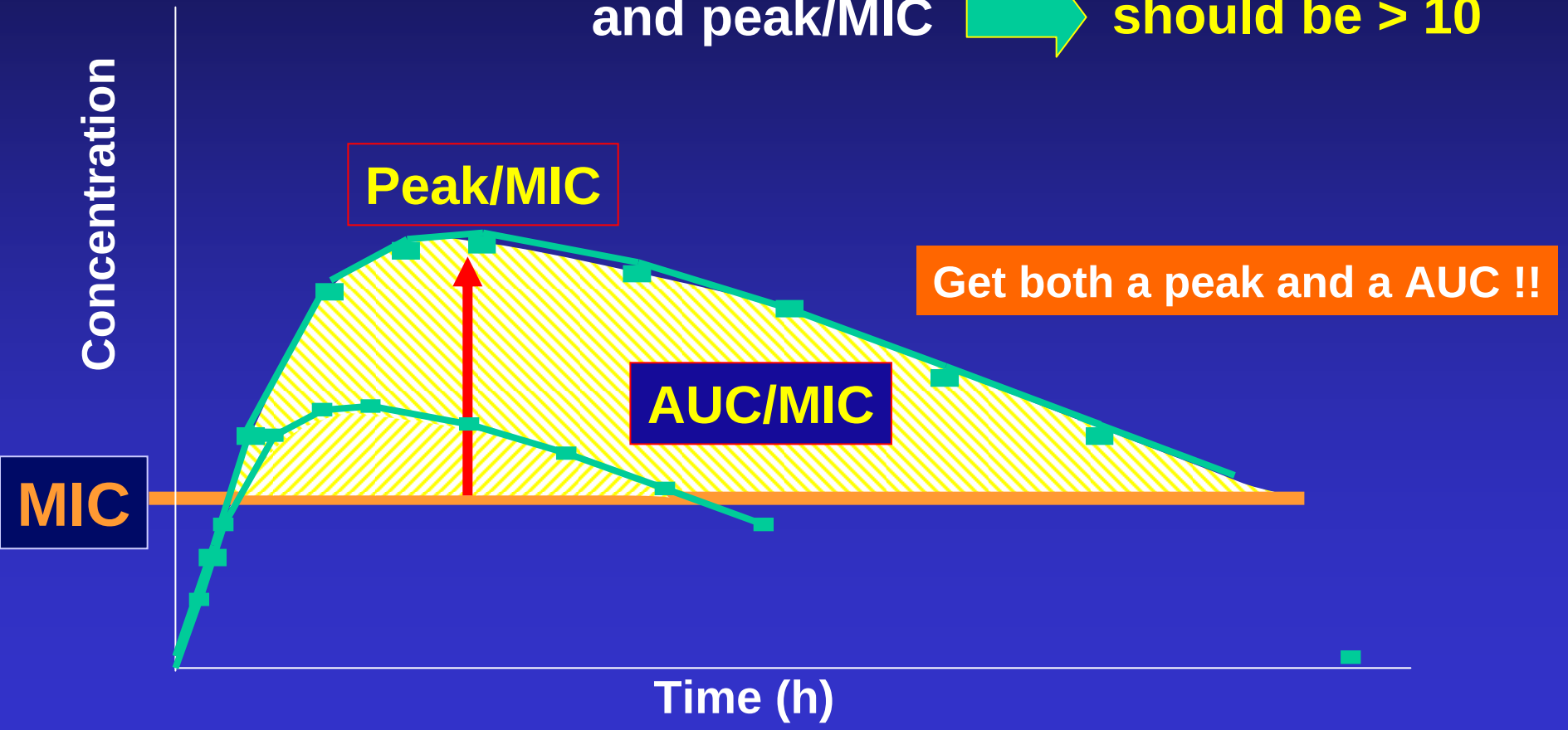
PK / PD breakpoints for AG

- **Genta, Netil, Tobra : 2 µg / ml**
- **Amika / Isépa : 4 µg / ml**

Fluoroquinolones: get a peak and an AUC !

increase the amount administered,
in order to optimize AUC/MIC → **should be > 125**

and peak/MIC → **should be > 10**



MIC data: J. Verhaegen et al., 2001

How to optimize the AUC / CMI ratio ?

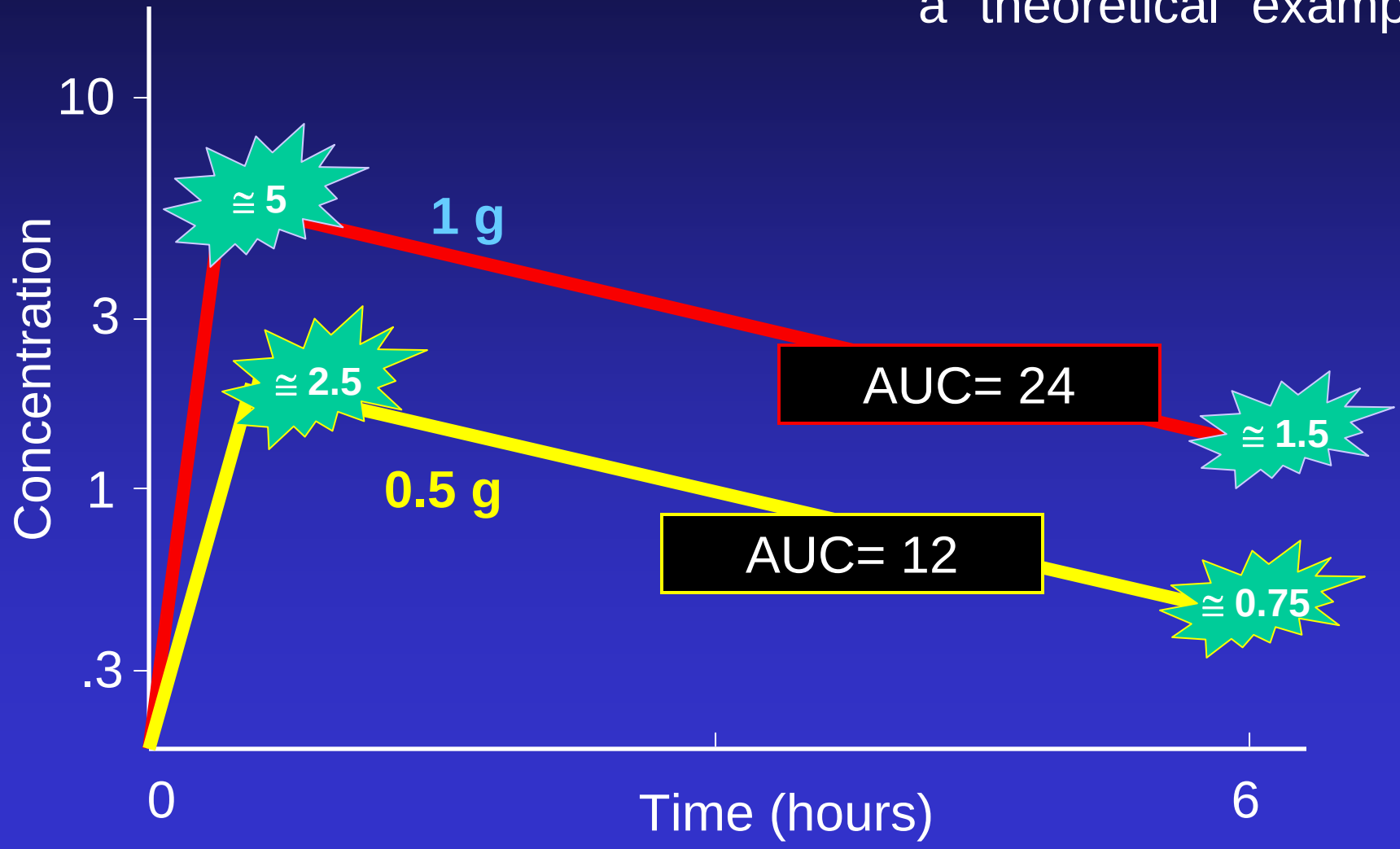
AUC = dosis / Cl

Adjust the daily dosis
~ target AUC

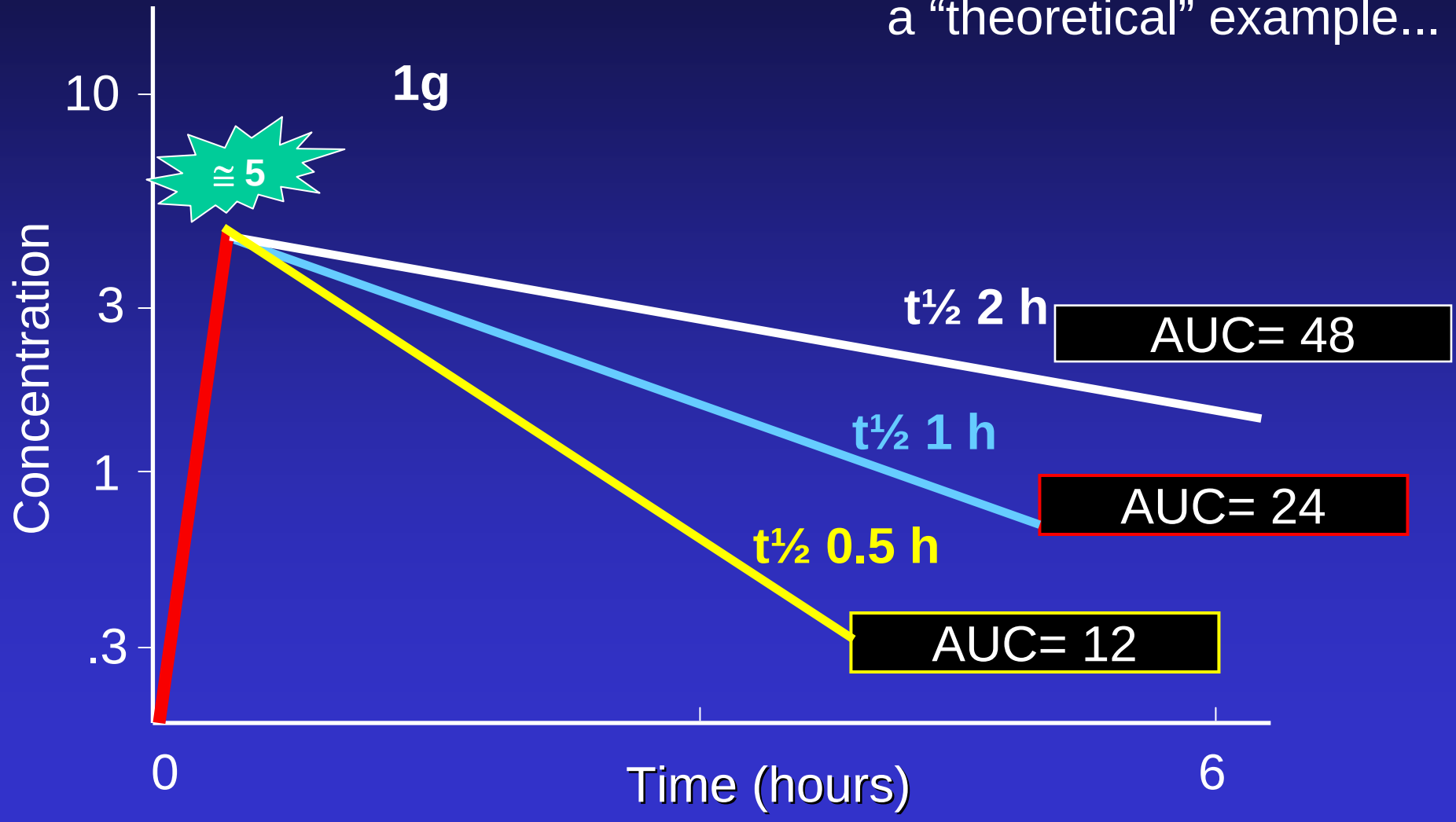
Adapt the number of administrations
~ pharmacokinetics of the drug

AUC and peak after one dose are directly related to this dose

a “theoretical” example...

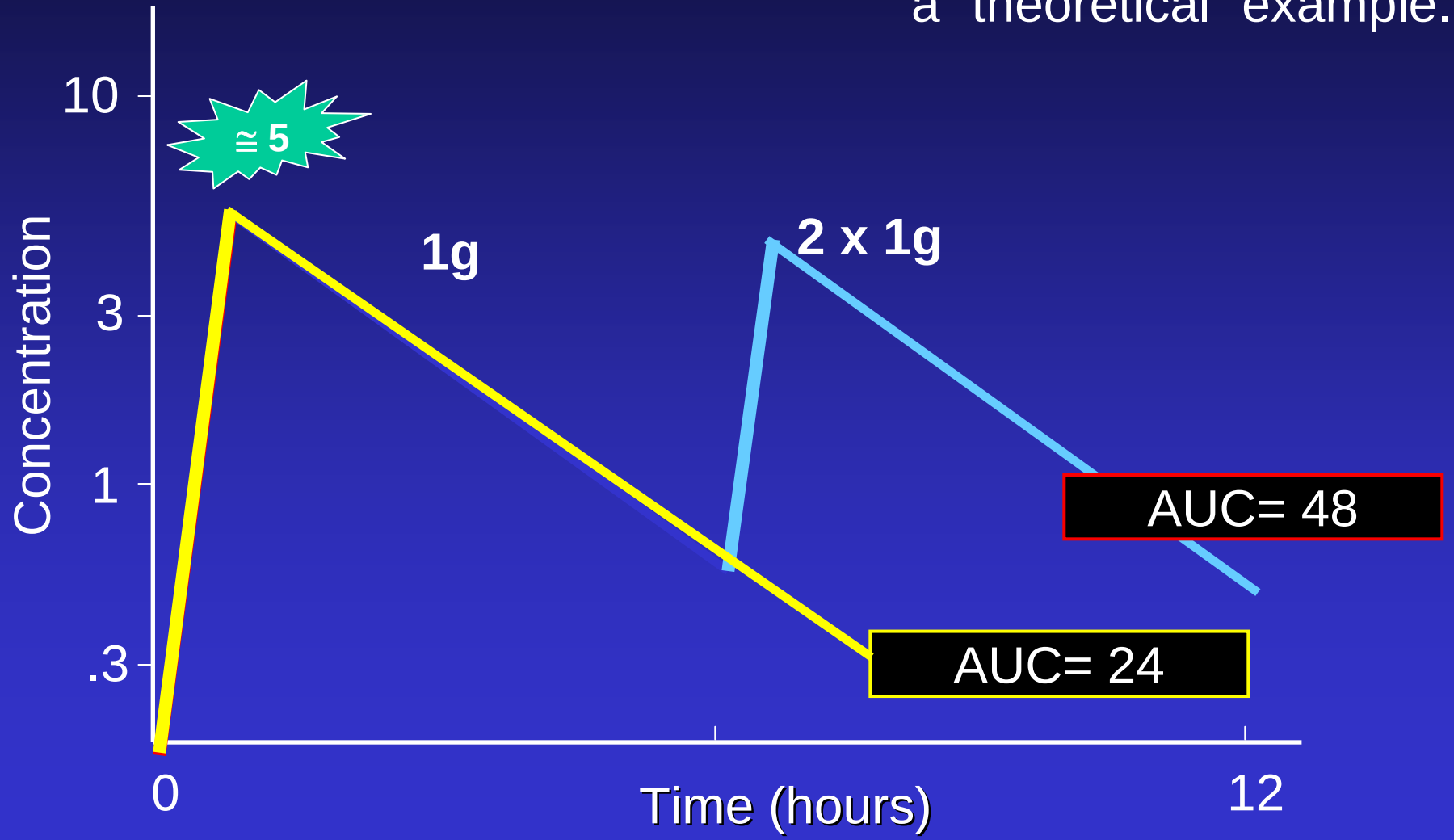


24h-AUC is inversely related to the drug clearance (BUT so is NOT the peak …)



24h-AUC is correlated to the number of unit doses (BUT, again, so is NOT the peak …)

a “theoretical” example...



PK/PD of fluoroquinolones in a nutshell

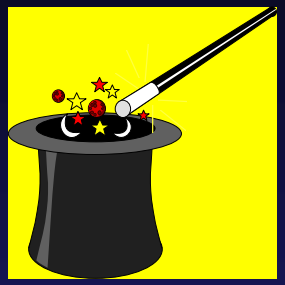
Remember:

- 24h-AUC is proportional to the daily dose
- peak is proportional to the unit dose...

- get a **24h-AUC /MIC > 125**, **and**
- get a **peak / MIC ratio > 8**

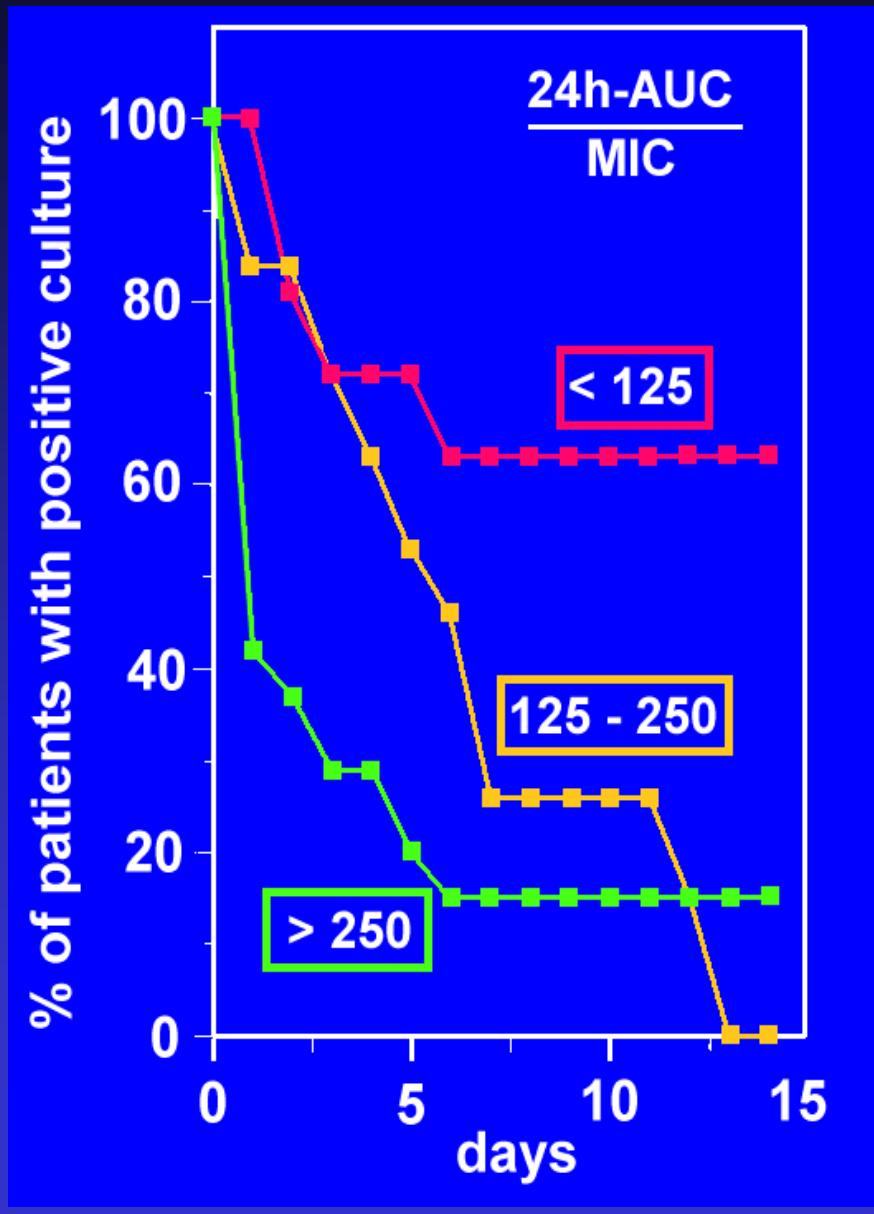
→ efficacy

- get this with the total daily dose and the appropriate unit dose …



AUC / MIC = 125 : a magic number ?

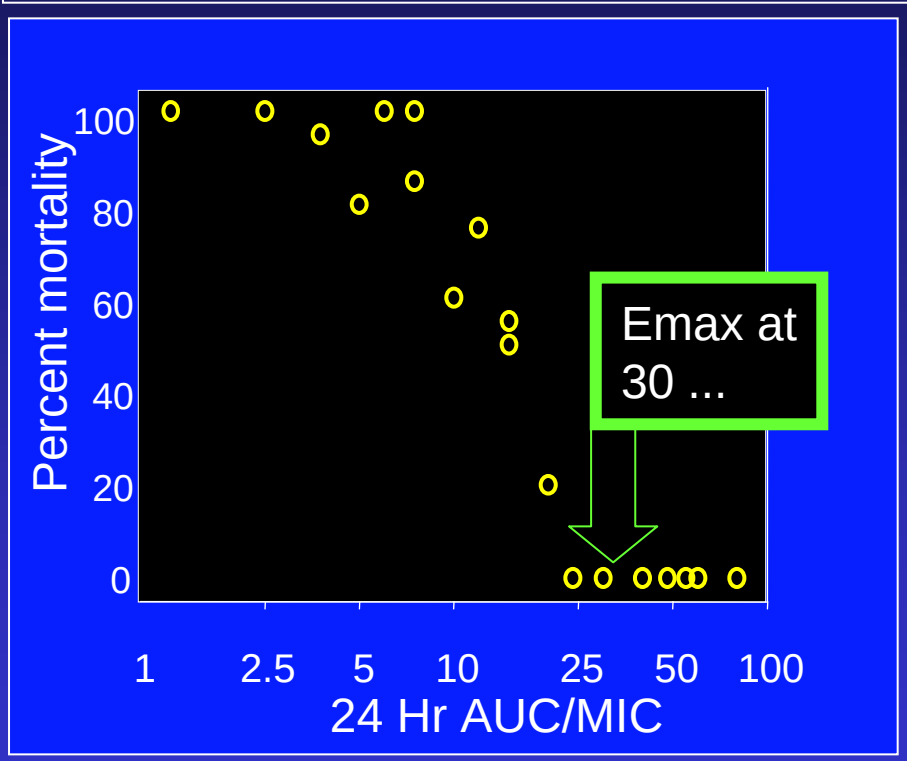
Patients respond to quinolones as a function of the 24 h-AUC of the quinolone they receive and the MIC of the offending organism
(example for Gram - infections seen in the "Methods")



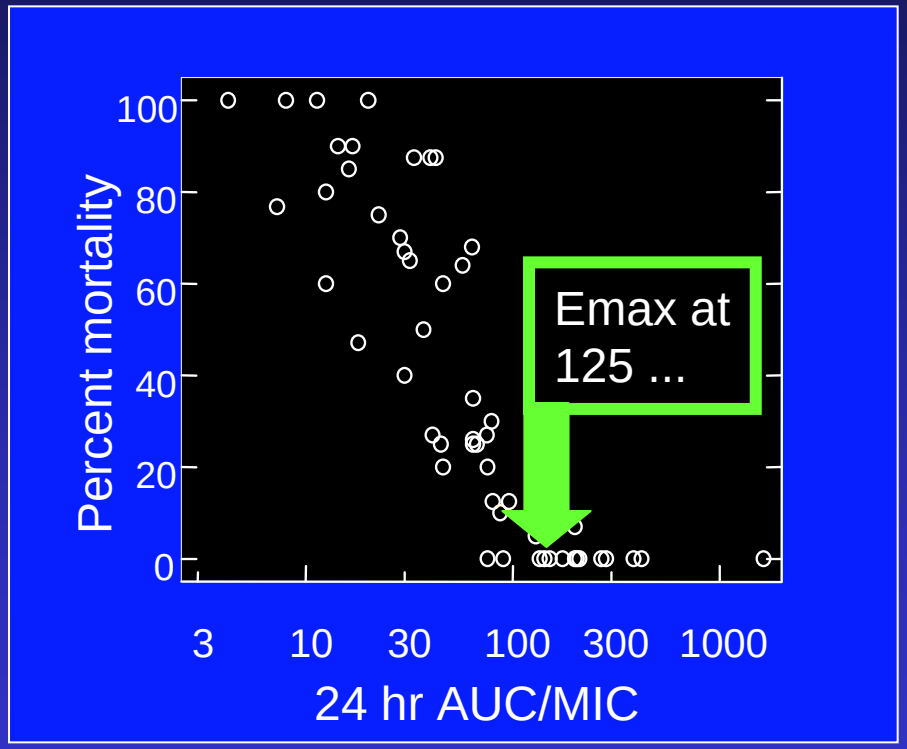
Forrest et al (1993) AAC 37:1073-81.

But remember that, for Gram (+), the immune status is critical ... (as seen in the methods)

Relationship Between 24 Hr AUC/MIC and Mortality for Fluoroquinolones against *S. pneumoniae* in Immunocompetent vs. Immunocompromised animal Models



non-neutropenic



neutropenic

Adapted from W.A. Craig : 7th ISAP Educational Workshop, San Diego, CA, 2002

Defining PK/PD breakpoints for fluoroquinolones

Drug	Dosage	PK/PD Bkpts (mg/L)	
		AUC/MIC (mg/24h)	**peak / MIC** (24h)
norfloxacin	800	**0.1**	**0.2**
ciprofloxacin	500	**0.1**	**0.2**
ofloxacin	400	**0.2-0.4**	**0.3 - 0.4**
levofloxacin	500	**0.4**	**0.4 - 0.5**
moxifloxacin	400	**0.4**	**0.4**

Adjust the dosis to the MIC

Daily dosage of levofloxacin	AUC *	MIC for an $AUC_{24h}/MIC = 125$
250	28	0.2
500	56	0.4
1000	112	0.8

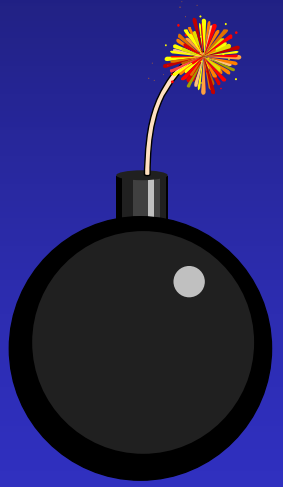
* based on normal half-lifes;
CL ~ 100 mg/dl
doses for an adult of 65 kg

But keep the unitary dose in the allowed limit …

Peak -related side effects :

SNC toxicity

Inhibition of CYP 450 activity
chondrotoxicity
phototoxicity



Choose the most active molecule

drug	Dosage (mg/24h)	AUC *	MIC for AUC/MIC = 125	MIC *S. pneumo*
ofloxacin	400	66	0.5	2
levofloxacin	500	73	0.4	1
ciprofloxacin	1000	40	0.3	0.5-2
moxifloxacin	400	48	0.4	0.01-0.5

PK/PD: take home message

1. For each drug, choose on a PK/PD basis the appropriate
   - scheme of administration
   - daily dosis

2. Adapt the dosage to the susceptibility of the target organism,
   - based on MIC data for the individual patient
   - based on local epidemiology

PK/PD : from today to tomorrow

today : applying these concepts
can help us to reach
an optimized efficacy

but let's prepare tomorrow:

how can we use this science
to avoid resistance development ?

Section 4 A